

Applicant : Don Fishbein  
Serial No. : 10/799,264  
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#### REMARKS

Claims 30-47 are pending and under examination. Applicant has hereinabove amended claims 30, 43 and 47. Support for the amendments to claim 30 can be found in the specification as originally filed at, inter alia, page 22, lines 14-16. Claim 43 has been amended to improve its grammar and claim 47 has been amended to correct its dependency.

#### Rejection of Claims 30-40 and 42-45 Under 35 U.S.C. §103(a)

In the October 17, 2008 Office Action, and as maintained in the October 6, 2009 Advisory Action, the Examiner rejected claims 30-40 and 42-45 under 35 U.S.C. §103(a) as allegedly obvious over Berger (U.S. Patent No. 6,090,799) in view of Schafer (U.S. Patent No. 4,456,596).

In response, applicant respectfully traverses the Examiner's rejection. Applicant notes, as explained previously, that the claims are directed to a method which is not predictable based on the prior art. However, in order to expedite prosecution, and without conceding the correctness of the Examiner's position, applicant has hereinabove amended claim 30, from which the remaining claims depend, to recite, in relevant part, that the weight gained is maintained at five weeks after discontinuation of oxandrolone administration.

#### Unexpected Results

The invention as now claimed is a method of effecting weight gain after weight loss resulting from post-burn catabolism in a patient wherein, inter alia, the weight gained is maintained at five weeks after discontinuation of oxandrolone administration. Berger does not teach or suggest maintenance

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of weight gain after discontinuation of oxandrolone administration. In fact, in the example given in Berger (see Col. 8, lines 19-22) "weight loss ensued" in the HIV-seropositive patient when unable to continue oxandrolone therapy. Thus the expectation from the prior art is weight loss after discontinuation of oxandrolone. The remaining cited art, in combination with Berger, does not alter this expectation. Moreover, the specification at page 22, lines 20-24 notes that muscle gain in body builders caused by anabolic agents "diminishes with the discontinuation of the drug" and contrasts this to the maintenance of weight observed with oxandrolone in burn victims. Accordingly, although the expectation from the art is of weight loss after discontinuation of oxandrolone, the claimed method is one showing maintenance of weight gained after discontinuation of oxandrolone. Thus, the method of promoting weight gain after weight loss resulting from post-burn catabolism as claimed possesses an unexpected and superior characteristic rendering it not obvious over the prior art.

#### Secondary Considerations

Long felt-need: Weight loss in burn victims has been long-recognized problem (for example, since at least 1973, see **Exhibits A-C**) and treating it has long been a therapy goal (see **Exhibits A-C**). In addition, oxandrolone had been available since 1964 and was known, as an anabolic steroid, to have growth effects. However, not until applicant's invention was oxandrolone used to treat weight loss in burn victims, i.e. more than twenty years after it had been established that weight loss in burn victims should be treated and it was known that oxandrolone was anabolic. Accordingly, absent impermissible hindsight, applicant maintains it is not

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reasonable to assert that the claimed method was "obvious" when those skilled in the art had apparently failed to find it obvious for over twenty years.

Differences with Prior Art

In their previous response, applicant pointed out that because of different etiologies of weight loss in subjects with HIV myopathy as compared to burn victims, it was not predictable that just because oxandrolone increased weight in a subject with HIV-myopathy that oxandrolone would also increase weight in a subject who had suffered post-burn catabolism. Berger teaches oxandrolone administration reverses weight loss in subjects with HIV-associated myopathy. Applicant maintains that because of different etiologies of weight loss in HIV myopathies as compared to burns victims (including hypermetabolism in burn victims) it was not predictable that just because oxandrolone increased weight in a subject with HIV-myopathy then it would also increase weight in a subject who had suffered post-burn catabolism. As applicant previously pointed out, weight gain will only occur if the increase exceeds the decrease, and the multiple causes of weight loss in burn victims, including tissue loss and hypermetabolism as well as increased metabolic rate, would render this unpredictable.

Accordingly, applicant respectfully requests reconsideration and withdrawal of this ground of rejection.

Rejection of claims 30 and 41 Under 35 U.S.C. §103(a)

The Examiner also rejected claims 30 and 41 under 35 U.S.C. §103(a) as allegedly obvious over Berger, as cited, in view of

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Schafer, as cited, and in further view of Labrie et al. (U.S. Patent No. 5,434,146). The Examiner asserted that Berger does not teach the administration of oxandrolone in a sustained release formulation but that Labrie et al. teach the administration of oxandrolone in a sustained release formulation. The Examiner alleged that in view of this it would have been prima facie obvious to one of ordinary skill in the art that the administration of an effective amount of oxandrolone in a sustained release formulation would effect weight gain after weight loss resulting from burn-induced trauma. The Examiner further stated that applicant argued that neither Berger nor Labrie et al. teach a sustained release formulation for oxandrolone. The Examiner asserted, however, that Labrie et al. do teach the sustained release of oxandrolone, citing Abstract, col. 21, lines 17 and 61-68 and col. 23, lines 20-24).

Applicant notes that, as set forth hereinabove, there is no teaching of the method of claim 30 in the combination of Berger and Schafer, and Labrie et al. does not cure this deficiency. In fact Labrie et al. does not teach weight gain therapies or subjects that have experienced a burn, but instead teaches treatment and prevention of estrogen-related diseases (see Abstract and Summary of Invention). The Examiner does assert that the Labrie et al. discloses administration of oxandrolone in a sustained release formulation. To the extent, *arguendo*, that Labrie et al. may teach a sustained release composition, it still does not teach a method of administration of oxandrolone to a patient for treating weight loss resulting from burn-induced trauma wherein the weight gained is maintained at five weeks after discontinuation of oxandrolone administration. Nor does it cure the other

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deficiencies of the combination of Berger and Schafer. Applicant maintains that the cited combined references do not teach or make obvious applicant's invention as claimed.

Thus, applicant maintains that claims 30-47 are not obvious over the combination of cited references. Accordingly, applicant respectfully requests that the Examiner reconsider and withdraw this ground of rejection.

**Claim 47**

Applicant notes that claim 47 is directed to a method, wherein the weight gained per unit time in the patient is "double the weight gained by a patient suffering weight loss resulting from burn-induced trauma receiving the protein supplement but not the oxandrolone."

No such method is taught in or suggested by the combination of Berger and Schafer. No such method is taught in or suggested by the combination of Berger, Schafer, Labrie et al. either. Moreover, the specific parameters of the method as claimed in claim 30 are not predictable from the prior art, especially in light of the effect of the increased metabolic rate seen in burn patients. In fact, the Examiner has acknowledged on page 4 of the Office Action that "the quantity and/or rate of" any actual weight gain would be affected, but has not offered any disclosure or reasoning as to how this effect would be predictable. Applicant therefore maintains that claim 47 is not obvious over the combinations of cited references.

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**SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT**

In accordance with the duty of disclosure under 37 C.F.R. §1.56, applicant directs the Examiner's attention to the following item, which is listed on the Form PTO-1449 (Substitute) attached hereto as **Exhibit D**. A copy of item 1 is attached hereto as **Exhibit 1**.

1. June 11, 2009 Office Action issued in connection with U.S. Serial No. 10/799,197. (**Exhibit 1**)

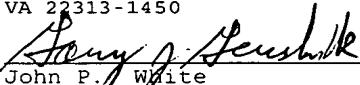
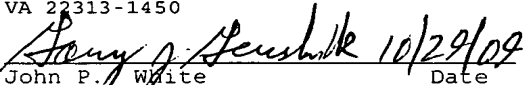
This Supplemental Information Disclosure Statement is being submitted under 37 C.F.R. §1.97(b)(4) before the issuance of a first Office Action after the filing of a Request for Continued Examination under §1.114. The Examiner is respectfully requested to make this item of record in the present application by initialing and returning a copy of the enclosed Form PTO-1449 (Substitute).

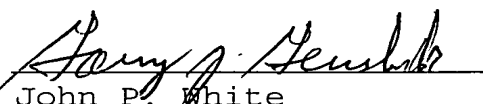
If a telephone interview would be of assistance in advancing prosecution of the subject application, applicant's undersigned attorney invites the Examiner to telephone him at the number provided below.

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No fee, other than the enclosed total fee of \$3,160.00, including \$2,350.00 for a five-month extension of time and \$810.00 for a Request for Continued Examination, is deemed necessary in connection with the filing of this Amendment and RCE. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:	
Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450	
 John P. White Reg. No. 28,678 Gary J. Gershik Reg. No. 39,992	 10/29/09 Date

  
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# **EXHIBIT A**



1: Am J Surg. 1976 Jun;131(6):722-4.

Complete enteral support of thermally injured patients.

Larkin JM, Moylan JA.

Total enteric nutritional support of thermally injured patients is a safe, effective means of providing adequate caloric and nitrogen requirements and avoiding the usual weight loss associated with burns. Protein and vitamin supplements and tube feeding, when indicated, are necessary adjuncts to the standard high protein, high calorie hospital diet. A team approach, consisting of physicians, nurses, dietitians, and patients, and careful daily monitoring of all parameters is essential to the success of this method.

PMID: 820213 [PubMed - indexed for MEDLINE]

#### Related Links

Oral hyperalimentation in the nutritional management of burned patients. [S Afr Med J. 1985] PMID:3922066

Nutritional evaluation of a blenderized diet in five major burn patients. [Am Surg. 1982] PMID:6816081

Nutrition guidelines for burned patients. [J Am Diet Assoc. 1986] PMID:3084608

Nutrition in the severely burned child. [Prog Pediatr Surg. 1981] PMID:6784187

Actual burn nutrition care practices. A national survey (Part II). [J Burn Care Rehabil. 1989] PMID:2496131

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**Exhibit A**

## **EXHIBIT B**

1: Surg Clin North Am. 1978 Dec;58(6):1151-6.

Nutritional support of the burned patient.

Curreri PW, Luterman A.

Patients with major thermal injury exhibit hypermetabolism as a result of neurohormonal alterations. Thus caloric requirements are exaggerated. Failure to provide supranormal caloric intake by both enteral and parenteral routes is associated with pronounced weight loss, delayed wound healing, decreased host resistance, and cellular dysfunction. Special dietary programs delivered early in the course of treatment must be utilized to prevent these complications of acute postburn malnutrition.

PMID: 104400 [PubMed - indexed for MEDLINE]

#### Related Links

Parenteral and enteral nutrition of the thermally injured patient. [Ann Chir Gynaecol. 1980] PMID:6781401

[Gastrointestinal dysfunction and peroral nutrition after severe burns] [Zhonghua Zheng Xing Shao Shang Wai Ke Za Zhi. 1992] PMID:1304954

[Problems in parenteral nutrition and metabolic support for burned patients] [Zhonghua Zheng Xing Shao Shang Wai Ke Za Zhi. 1992] PMID:1304953

Early enteral feeding of a severely burned pediatric patient. [J Burn Care Rehabil. 1994] PMID:8056824

Burn care. Metabolic alterations and nutritional management. [AACN Clin Issues Crit Care Nurs. 1993] PMID:8489885

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**Exhibit B**

## **EXHIBIT C**

# Weight Loss Following Thermal Injury

THOMAS W. NEWSOME, M.D., MAJOR, MC,\* ARTHUR D. MASON, JR., M.D.,  
BASIL A. PRUITT, JR., M.D., COL, MC

THE SEVERE WEIGHT LOSS frequently associated with thermal injury has been attributed to a combination of hypermetabolism and inadequate caloric intake. Energy expenditures as much as twice normal have been documented during the first 3 weeks after such injury,<sup>2,7</sup> and negative nitrogen balance may persist for 5-6 weeks.<sup>5</sup> At the same time, oral alimentation may be restricted by prolonged ileus, disorientation, facial burns, associated injuries, or the need for respiratory support via an endotracheal or tracheostomy tube. Prior to the recent development of technics for intravenous hyperalimentation, administration of nutrients by the venous route was also limited. Even with the administration of 4,000-8,000 calories per day by a combination of intravenous and oral routes, actual weight gain is seldom achieved in the first few weeks postburn, although weight stabilization may be attained.<sup>6</sup>

Most of the studies of this catabolic phase of burn injury have been confined to intensive but brief monitoring of oxygen consumption, evaporative water loss, and body weight in relatively small numbers of patients during the first 3 weeks postburn. Soroff's<sup>5</sup> study of nitrogen balance is the only long-term analysis of postburn metabolism and it was limited to patients with burn sizes of 20-35%.

In order to define the temporal pattern of postburn weight loss and determine its relation to burn size, we have divided a selected patient population according to burn size and analyzed their weight changes over a 3-month postburn period.

## Methods

A retrospective analysis was made of the weight records of 1,028 patients admitted to the United States

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Brooke Army Medical Center,  
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Army Institute of Surgical Research burn unit between December 1967 and November 1970. This time period was chosen because it immediately preceded the initiation of high caloric parenteral feedings. Eighty-six patients with reliable preburn weights, serial weight assessments postburn, and without major amputations were consolidated into three burn-size ranges of 0-19% (17 patients), 20-39% (25 patients), and 40+% (44 patients). Patient ages ranged from 2-70 years with the greatest number in the 15-40 year range.

Each patient had been weighed on a Toledo 100 Kg. scale with 50 Gm. graduations. Weekly weights from the time of admission to the eighth week postburn were recorded in the 0-19% and 20-39% ranges. At 12 weeks postburn no patients with burns under 20% and only four patients with 20-39% burns remained hospitalized. Hospital discharges occurred later in patients with burns of more than 40% and weight data of this group were recorded at 12 weeks. Those weights obviously biased by dressings were discarded. For comparison, all weights were expressed as per cent of preburn weight.

For each time period, the three data groups were subjected to a preliminary analysis of variance. In those periods where significant ( $p < 0.05$ ) intergroup differences were detected, all possible comparisons of differences between individual groups were tested for significance ( $p < 0.05$ ) by the technic of Scheffe.<sup>4</sup>

Hospital records were also used to determine, for each burn size group, the mean date of wound coverage by reepithelialization and/or autografting.

## Results

Figure 1 shows a distinct pattern of weight loss following thermal injury in which both extent and duration of loss are proportional to burn size.

Submitted for publication August 31, 1972.

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Request reprints: Library Branch, US Army Institute of Surgical Research, Brooke Army Medical Center, Fort Sam Houston, Texas 78234.

In the 17 patients with burns covering less than 20% of the total body surface, mean weight loss was 3.5% one week postburn. The maximum loss of 6% occurred 3 weeks after injury. Weight gain began at the fourth week and return to preburn weight was recorded at 8 weeks. Wound coverage in this group was attained at a mean time of 33 days postburn.

In 25 patients with burn sizes from 20–39%, significant weight loss did not appear until the second week postburn (6%) and the maximum decrease of 12% was not reached until the end of the fourth week. Modest weight gains were noted at 6 and 8 weeks. Mean time of wound coverage in this group was the fortieth postburn day.

In the 44 patients with burns of more than 40% there was a 4% weight loss at 1 week, a 10% loss at 2 weeks, and a continuing loss until a maximum of 22% was reached at 8 weeks. In the survivors still hospitalized 12 weeks after injury there was a wide range of weight loss, but the mean weight loss was smaller than at 8 weeks. Wound coverage was completed at a mean time of 57 days postburn in this group.

Statistical analysis of intergroup weight differences demonstrated persistent significant difference between the mean per cent of preburn weight of patients with burns of under 20% and that of patients with burns of over 40% at all times beyond the first week postburn. The difference between patients with less than 20% burns and those with 20–39% burns did not achieve significance until the fourth week, while the difference between the latter group and patients with greater than 40% burns was not significant until the eighth week.

Examination of the weight curves (Fig. 1) reveals that weight stabilization occurred approximately 2 weeks prior to completion of wound coverage in both the 0–19% and 20–39% groups and that 2 weeks prior to wound closure in the 40+% group the rate of weight loss flattened. Weight gain was subsequently associated with wound closure in all groups.

### Discussion

These data define a temporal pattern of weight loss following thermal injury in which the magnitude and duration of loss are directly related to the severity of injury.

A metabolic study closely paralleling this review is that of Soroff<sup>5</sup> in which nitrogen balance was carefully monitored over a 3-month period in 11 patients with burn wounds of from 20 to 35% of the total body surface. Although nitrogen requirements did not return to control levels until 60–70 days postburn, a positive cumulative nitrogen balance was reached between 30–39 days with the use of high protein dietary supplements.

TABLE 1. Intergroup Statistical Comparisons

Postburn Week	A-C	A-B	B-C
1	NS	NS	NS
2	*	NS	NS
3	*	NS	NS
4	**	*	NS
6	*	NS	NS
8	**	*	*

Group A—0–19% burns

Group B—20–39% burns

Group C—40 + % burns

Significance: NS—not significant

\*— $0.01 < p < 0.05$

\*\*— $0.001 < p < 0.01$

This latter figure correlates reasonably well with the 28-day point at which the mean weight stabilized in our study group with burns of from 20 to 39% of the total body surface. The failure of this group to achieve more than modest weight increase over the next 4 weeks may confirm the persistence of significant catabolism suggested by Soroff's data.

The relation of wound closure to postburn metabolic rates has been the focus of several studies which have documented concomitant increases in both oxygen consumption and evaporative water loss in the early weeks postburn.<sup>1–3,7</sup> Because of the calculated magnitude of daily evaporative water loss from the burn wound into a normally humidified environment (2 Gm./Kg./% burn<sup>8</sup>) and the measured heat cost of vaporization of 0.58 calories/Gm. at 30°C., a causal relationship between evaporative loss and postburn hypermetabolism has been hypothesized. This does not, however, appear to be a simple relationship, for Zawacki, *et al.*<sup>9</sup> have shown that diminishing evaporative loss over a 12-hour period does not alter the metabolic rate. Gump

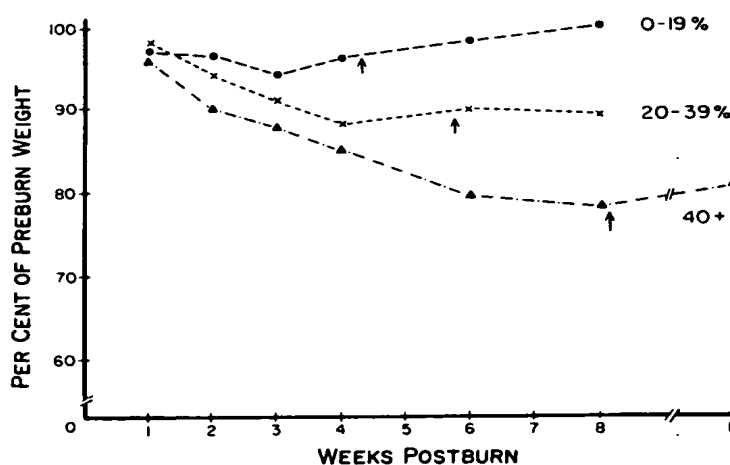


FIG. 1. Mean weight following thermal injury in three burn size ranges is plotted as a per cent of preburn weight. Arrow mark the mean time of wound closure for each range.

and Kinney<sup>2</sup> have presented additional data suggesting that while evaporative losses decline during the first 2 weeks, the metabolic rate rises. In contrast is a report from Sweden<sup>1</sup> that postburn metabolic rates are decreased by a warm, dry environment which may provide a portion of the heat required for vaporization. Clouding interpretation of this study is the fact that the control temperature of 22°C. used for contrast is sufficiently low to enhance pretreatment hypermetabolism.

Definitive wound closure, defined as the completion of reepithelialization and/or autografting of the burn wound, followed weight stabilization by almost 2 weeks in each of the burn size ranges considered. At the time when reversal of weight loss occurred, however, coverage of significant portions of the burn wound had already been effected in most patients by a combination of reepithelialization of second degree burn and allografting of third degree burn. Whether such closure bears a causal relationship to the reversal of weight loss cannot be determined from our data, since the patient groups did not include individuals in whom such coverage was deliberately delayed. Our data do show that final wound closure, like weight stabilization, occurs later as burn size increases.

Metabolic stimuli other than the open wound are active in the burn patient and probably relate to burn size. Among these are hyperdynamic circulation, elevated catecholamines, and sepsis. As the burn wound heals, these ebb, and the patient's metabolic demands diminish.

Since both the magnitude and the duration of the catabolic phase following burn injury seem clearly related to the extent of injury and are difficult to effec-

tively mute, emphasis must be placed on supplying the patient with a caloric intake adequate to achieve net caloric balance. The effectiveness of vigorous oral and intravenous caloric support has been the subject of a recent report from this institute by Wilmore, et al.<sup>6</sup>

### Summary

A pattern of weight loss has been found in patients with thermal injuries. The magnitude and duration are directly related to the extent of injury. A maximum mean loss of 22% of preburn weight occurred 8 weeks postburn in patients with burns covering more than 40% of the total body surface. Weight stabilization preceded definitive wound closure and was considered to reflect diminishing metabolic demands.

### References

1. Barr, P.-O., Liljedahl, S.-O., Birke, G. and Plantin, L.-O.: Oxygen Consumption and Water Loss During Treatment of Burns with Warm Dry Air. *Lancet*, 1:164, 1968.
2. Cump, F. E. and Kinney, J. M.: Energy Balance and Weight Loss in Burned Patients. *Arch. Surg.*, 103:442, 1971.
3. Harrison, H. N., Moncrief, J. A., Duckett, J. W., Jr. and Mason, A. D., Jr.: The Relationship Between Energy Metabolism and Water Loss from Vaporization in Severely Burned Patients. *Surgery*, 56:203, 1964.
4. Ostle, B.: *Statistics in Research*, Iowa State College Press, 1958.
5. Soroff, H. S., Pearson, E. and Artz, C. P.: An Estimation of the Nitrogen Requirements for Equilibrium in Burned Patients. *Surg. Gynecol. Obstet.*, 112:159, 1961.
6. Wilmore, D. W., Curreri, P. W., Spitzer, K. W., Spitzer, M. E. and Pruitt, B. A., Jr.: Supranormal Dietary Intake in Thermally Injured Hypermetabolic Patients. *Surg. Gynecol. Obstet.*, 132:881, 1971.
7. Zawacki, B. E., Spitzer, K. W., Mason, A. D., Jr. and Johns, L. A.: Does Increased Evaporative Water Loss Cause Hypermetabolism in Burned Patients? *Ann. Surg.*, 171:236, 1970.

# **EXHIBIT D**



# **EXHIBIT 1**